Research Article

Photocatalytic Deoxygenation of Sulfoxides Using Visible Light: Mechanistic Investigations and Synthetic Applications

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ABSTRACT: The photocatalytic deoxygenation of sulfoxides to generate sulfides facilitated by either $Ir[(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ or $fac\text{-}Ir(ppy)_3$ is reported. Mechanistic studies indicate that a radical chain mechanism operates, which proceeds via a phosphoranyl radical generated from a radical/polar crossover process. Initiation of the radical chain was found to proceed via two opposing photocatalytic quenching mechanisms, offering complementary reactivity. The mild nature of the radical deoxygenation process enables the reduction of a wide range of functionalized sulfoxides, including those containing acid-sensitive groups, in typically high isolated yields.

KEYWORDS: sulfoxide, deoxygenation, reduction, radical, visible light, photoredox catalysis, sulfide radical cation
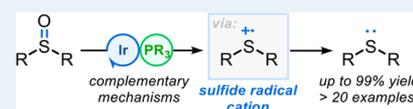
The deoxygenation of sulfoxides to generate sulfides is a fundamental transformation in organic synthesis[1] and biochemistry.[2] Established methods to convert sulfoxides into sulfides[3] involve the use of low-valent metallic species,[4] metal hydride reagents,[5] halide ions,[6] and phosphorus compounds.[7] However, these reaction systems can suffer from potential disadvantages, including the use of expensive and/or toxic reagents, difficult workup procedures, and use of harsh reaction conditions, which often limit their functional group tolerance. Consequently, this is an area of continued research, and new, efficient procedures for the reduction of sulfoxides into their corresponding sulfides are desirable.

Over the past decade, photoredox catalysis has evolved into a vitally important method able to address long-standing challenges in synthetic chemistry,[8] in large part due to the mild conditions by which reactive radicals can be generated. However, photocatalytic methods for deoxygenation of sulfoxides have rarely been explored.[9] The cleavage of C−O bonds via β-scission of phosphoranyl radicals was initially recognized in the early 1970s by Bentrude,[10] and since then, the groups of Zhu and Xie,[11] Doyle,[12] and Rovis[12] have extended the synthetic application of this strategy to incorporate photoredox catalysis (Figure 1A), establishing valuable methods for deoxygenation of alcohols and carboxylic acids. More recently, this work was extended to include cleavage of N−O bonds by Yang et al.[13] and also by Lardy and Schmidt,[14] who employed more traditional radical initiation methods.

Inspired by these works, we speculated that direct cleavage of S=O bonds could be accomplished via a polar/radical crossover process between phosphine radical cations, generated from a photocatalyst (PC) initiator, and sulfoxides, resulting in mild deoxygenation of sulfoxides (Figure 1B). Based on existing phosphoranyl radical studies (Figure 1A)
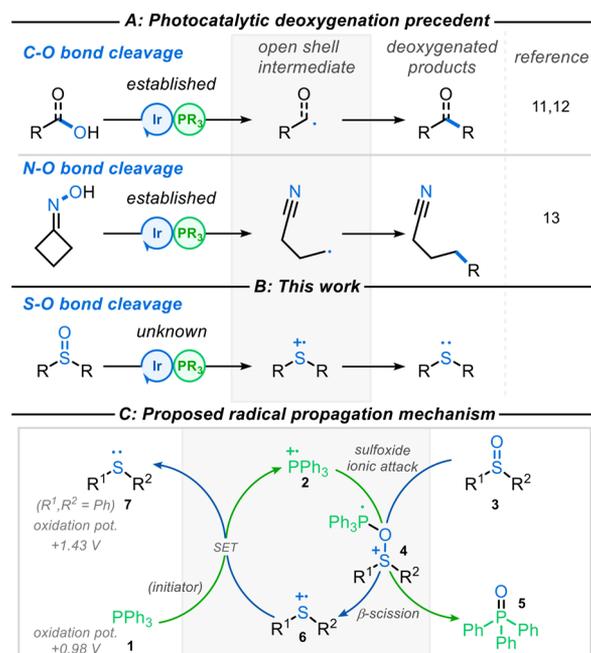

Figure 1. Photocatalytic deoxygenation methods.

and the reported oxidation potentials of sulfides (e.g., diphenyl sulfide {$E_{1/2}$ = +1.43 V versus saturated calomel electrode
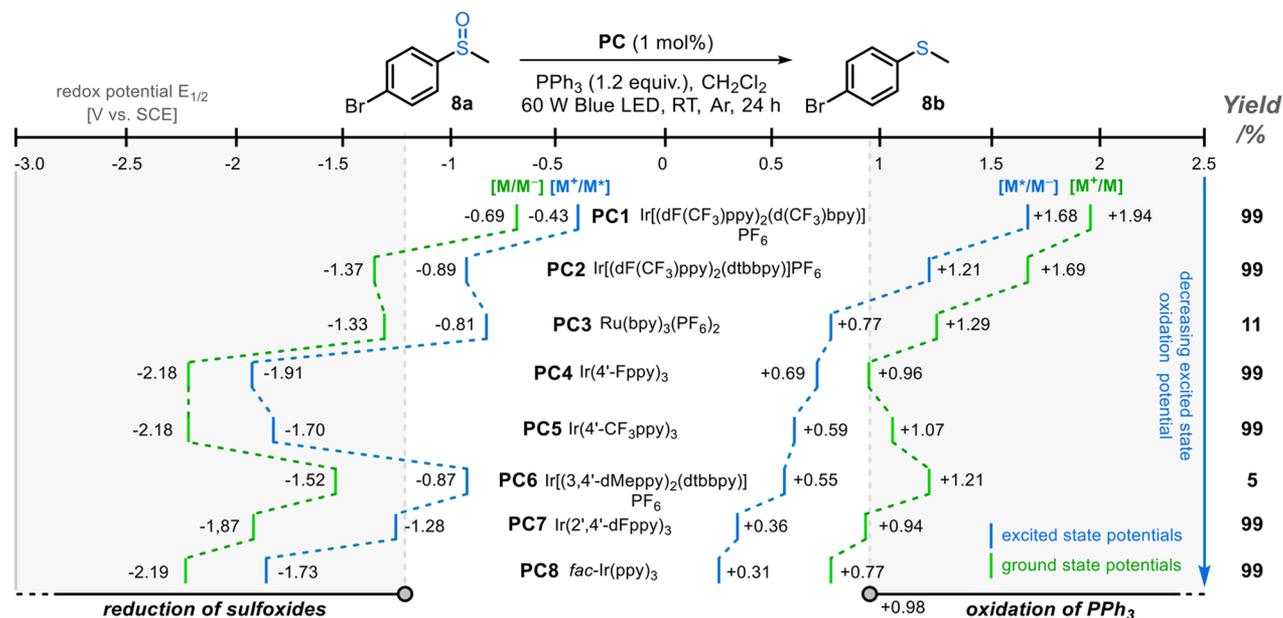
Scheme 1. Photocatalyst Initiator Screening

Table 1. General Reaction Condition Optimization[a]

entry	deviation from standard conditions	yield (PC2) (%)	yield (PC8) (%)
1	none	99	99
2	no PC	0	0
3	no light	0	0
4	no PPh$_3$	0	9
5	3 equiv of TEMPO	2	3
6	under air	69	46
7	THF	85	69
8	toluene	44	99
9	PCy$_3$	48	33
10	PPh$_2$OEt	68	5
11	P(OPh)$_3$	28	8

[a]Reaction conditions: **8a** (0.20 mmol), **PC2** or **PC8** (1 mol %), PPh$_3$ (0.24 mmol) in CH$_2$Cl$_2$ (1.0 mL) at RT, 24 h. ^{1}H NMR yields reported based on a trimethoxybenzene internal standard.

[SCE]})[15] relative to those of phosphines (e.g., PPh$_3$ {$E_{1/2}$ = +0.98 V versus SCE}),[12] a radical chain mechanism was proposed[16] (Figure 1C, see later for a description).

We postulated that initiation of a radical chain deoxygenation process could be promoted by single-electron oxidation of PPh$_3$ **1** using a suitable oxidizing photocatalyst (initiator)[17] to afford a catalytic amount of phosphine radical cation **2**. Polar nucleophilic addition of sulfoxide **3** to radical cation **2** would generate phosphoranyl radical **4**, which upon β-scission, would afford sulfide radical cation **6** and triphenylphosphine oxide **5**. Finally, reduction of the sulfide radical cation **6** by PPh$_3$ **1** would afford the desired sulfide **7**, as well as propagating the radical chain via regeneration of phosphine radical cation **2**. Herein, we describe the realization of this radical chain process for the high-yielding deoxygenation of sulfoxides under mild, visible light-driven reaction conditons.[18]

Scheme 2. Initiation via Phosphine Oxidation (PC2)
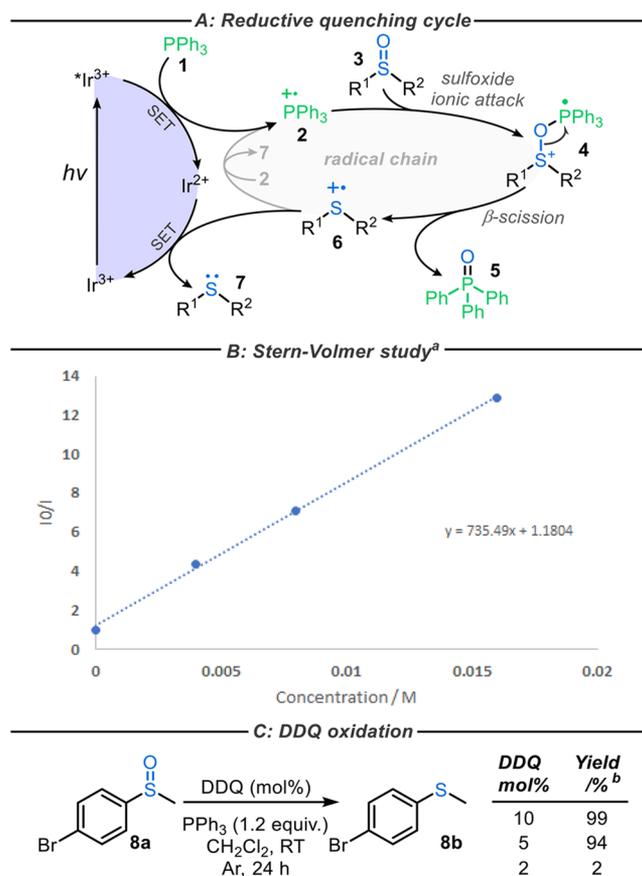
[a]Stern−Volmer quenching study of Ir[(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ with PPh$_3$ in degassed CH$_2$Cl$_2$. [b]^{1}H NMR yields reported based on a trimethoxybenzene internal standard.

Studies began by surveying the ability of a series of photocatalyst initiators (**PC1**−**PC8**, Scheme 1) to promote the reduction of 4-bromophenyl methyl sulfoxide **8a** into sulfide **8b** using PPh$_3$ as the terminal reductant and CH$_2$Cl$_2$ as

Scheme 3. Initiation via Adduct Reduction (PC8)

A: Oxidative quenching cycle

B: Stern-Volmer study[a]

$y = 0.0161x + 0.9551$

C: Cyclic Voltammetry

— DCM + electrolyte
— DCM + electrolyte + PPh₃
— DCM + electrolyte + sulfoxide **8a**
— DCM + electrolyte + PPh₃ + sulfoxide **8a**
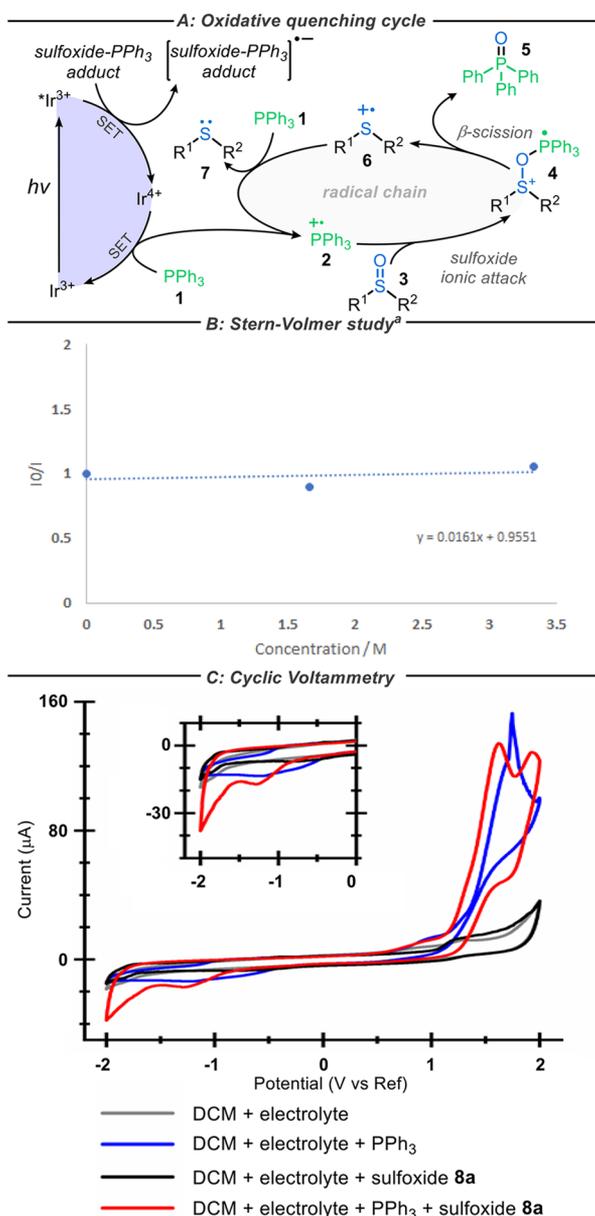
[a]Stern−Volmer quenching study of *fac*-Ir(ppy)₃ with 1:1 solution of sulfoxide **8a**:PPh₃ in degassed CH₂Cl₂.
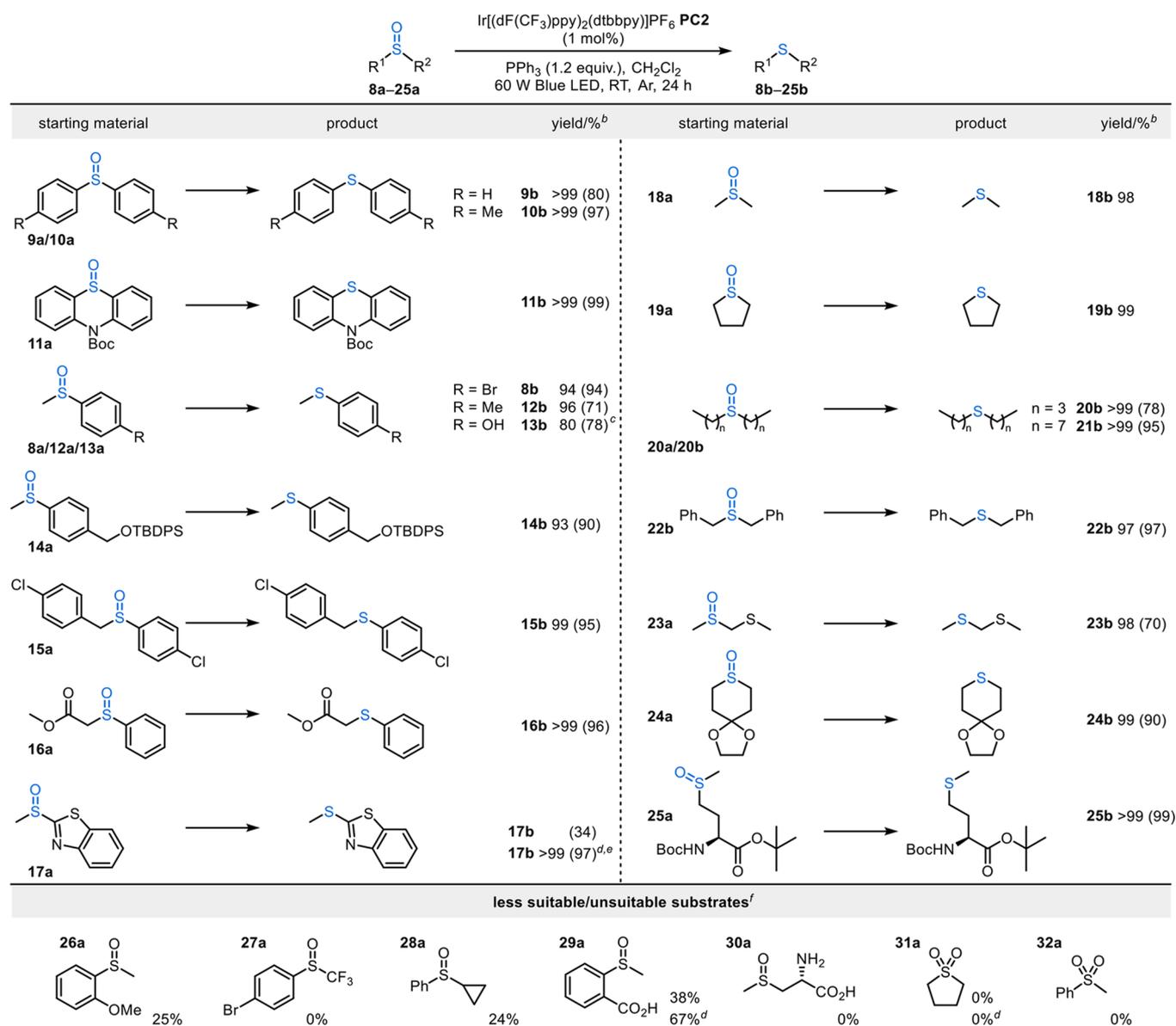
the solvent, irradiating with a 60 W blue LED light[19] under an argon atmosphere. In line with related literature,[11,12] both **PC1** and **PC2**, which have excited-state oxidation potentials (M*/M⁻) greater than that of PPh₃ ($E_{1/2}$ = +0.98 V versus SCE), afforded sulfide **8b** in excellent yields.[20] Moreover, **PC3** and **PC6**, which have excited-state oxidation potentials lower than PPh₃, resulted in much lower yields of sulfide **8b** (11 and 5%, respectively) as expected. However, PCs possessing a far lower oxidation potential than PPh₃ (e.g., **PC7** and **PC8**; the PCs that we originally considered to be the least likely to promote effective deoxygenation of **8a**) unexpectedly promoted the formation of sulfide **8b** in high yields. We noticed that all four PCs (**PC4**, **PC5**, **PC7**, and **PC8**) are able to initiate the reaction effectively despite their low excited-state oxidation potentials and relatively high excited-state reduction potentials (M⁺/M*). In contrast, the PCs with relatively low excited-state oxidation and reduction potentials (i.e., **PC3** and **PC6**, for

which both potentials are within the white area in Scheme 1) did not perform well in the reaction. These observations suggested that two mechanistic pathways may be viable, based on either a reductive or oxidative photocatalyst quenching cycle, with the route taken dependent on the redox potentials of the PC initiator used.

To probe this possibility further, comparative control reactions were conducted, with Ir[(dF(CF₃)ppy)₂(dtbbpy)]-PF₆ (**PC2**) chosen as a representative oxidizing photocatalyst and *fac*-Ir(ppy)₃ (**PC8**) as a representative reducing photocatalyst. In the absence of PC and light (entries 2 and 3, Table 1), no reaction occurred in either system. In the absence of PPh₃, no reaction occurred when employing the oxidizing **PC2**, although contrastingly, a small amount of conversion into sulfide **8b** was observed when employing the reducing **PC8**. TEMPO drastically suppressed the efficiency of both reaction systems, supporting a free-radical reaction pathway (entry 5); triphenylphosphine oxide was the major product formed in these TEMPO reactions, presumably via the pathway described by Bentrude.[10] Both reactions could be performed in other solvents or under an atmosphere of air but a reduction in yield was generally observed (entries 6−8). Other readily available phosphines, phosphites, and phosphinites were also able to promote sulfoxide reduction, albeit in reduced yields compared with PPh₃ (entries 9−11).

Mechanistically, the single-electron oxidation of PPh₃ by the most oxidizing catalysts (e.g., **PC1** and **PC2**, Scheme 1) is an established concept.[11,12] Consequently, initiation of the radical chain cycle when using such oxidizing PCs is proposed to occur via reductive quenching of the excited-state PC to generate the key phosphorus radical cation **2** required to initiate the proposed radical chain mechanism (Scheme 2A). To support this, Stern−Volmer quenching studies were conducted, confirming that the emission of the excited-state **PC2** is quenched by PPh₃ (Scheme 2B). Furthermore, when DDQ, an organic oxidant, was used in sub-stoichiometric amounts (≥5 mol %) in place of the PC, sulfide **8b** was produced in excellent yields (Scheme 2C), further supporting the notion that the generation of phosphorus radical cation **2** promotes an efficient radical chain process, as depicted in Figure 1C.

In contrast, PCs possessing lower oxidation potentials (M*/M⁻) such as *fac*-Ir(ppy)₃ (**PC8**) should not be able to oxidize PPh₃, which is supported by the absence of emission quenching of the excited state of **PC8** by PPh₃ (see the Supporting Information). It has also been documented that sulfoxides such as DMSO are unable to quench the emission of **PC8**.[21] Nonetheless, contrary to these observations, which suggest that no reaction should occur, it was found that DMSO can be reduced to DMS in high yields (99%) when reacted with **PC8** and PPh₃ under our standard reaction conditions (for conditions, see Table 1). We initially postulated that this may be a result of energy transfer from the excited state of **PC8** to the sulfoxide,[22] thus forming an excited-state sulfoxide species able to undergo deoxygenation. The low-yielding deoxygenation of **8a** in the absence of PPh₃ (see earlier control reactions, entry 4, Table 1) offers some support for this hypothesis, and the direct deoxygenation of sulfoxides under UV irradiation has also been reported.[23] However, we could find no evidence of emission quenching of the excited state of **PC8** by either sulfoxides **8a** or **18a** in Stern−Volmer quenching studies (in line with literature precedent).[21] Furthermore, if energy transfer is involved, it is not clear

Scheme 4. Substrate Scope of Sulfoxide-to-Sulfide Reduction[a]

Reaction scheme:

$$R^1\text{-S(O)-}R^2 \quad \xrightarrow[\text{PPh}_3\ (1.2\ \text{equiv.}),\ CH_2Cl_2,\ 60\ W\ \text{Blue LED, RT, Ar, 24 h}]{\text{Ir[(dF(CF}_3)\text{ppy)}_2(\text{dtbbpy})]\text{PF}_6\ \textbf{PC2}\ (1\ \text{mol}\%)} \quad R^1\text{-S-}R^2$$

8a–25a → **8b–25b**

starting material	product	yield/%[b]	starting material	product	yield/%[b]
9a/10a		R = H 9b >99 (80) / R = Me 10b >99 (97)	18a		18b 98
11a (Boc)	(Boc)	11b >99 (99)	19a		19b 99
8a/12a/13a		R = Br 8b 94 (94) / R = Me 12b 96 (71) / R = OH 13b 80 (78)[c]	20a/20b		n = 3 20b >99 (78) / n = 7 21b >99 (95)
14a (OTBDPS)	(OTBDPS)	14b 93 (90)	22b		22b 97 (97)
15a		15b 99 (95)	23a		23b 98 (70)
16a		16b >99 (96)	24a		24b 99 (90)
17a		17b (34) / 17b >99 (97)[d,e]	25a (BocHN)	(BocHN)	25b >99 (99)

less suitable/unsuitable substrates[f]

26a	27a	28a	29a	30a	31a	32a
(OMe) 25%	(Br, CF3) 0%	Ph, cyclopropyl 24%	(CO2H) 38% / 67%[d]	(NH2, CO2H) 0%	0%[d]	(Ph) 0%

[a]Reaction conditions: sulfoxide (0.30 mmol), Ir[(dF(CF$_3$)ppy)$_2$(dtbpy)]PF$_6$ (1 mol %), PPh$_3$ (0.36 mmol) in CH$_2$Cl$_2$ (1.5 mL) at RT, 24 h. [b]^{1}H NMR yields reported based on a trimethoxybenzene internal standard; isolated yields of products after column chromatography are reported in parentheses. [c]1 mol % Ir[(dF(CF$_3$)ppy)$_2$(d(CF$_3$)bpy)]PF$_6$ (**PC1**) and 4 day reaction time employed. [d]1 mol % *fac*-Ir(ppy)$_3$ (**PC8**). [e]48 h reaction time employed. [f]Yields of the corresponding sulfide observed by ^{1}H NMR spectroscopy based on a trimethoxybenzene internal standard are presented.

why the redox properties of the various PCs would have such a pronounced influence on the observed reactivity. Based on these observations, it was considered more likely that initiation is mediated by a redox process. It is also clear from the synthetic results that phosphine plays a key role in the reaction. Thus, an alternative mechanism was postulated, in which PPh$_3$ and the sulfoxide interact to form an adduct that can initiate the radical chain mechanism via an initial oxidative quench of the PC (Scheme 3A).

This alternative mechanism would proceed via an electron transfer from the excited-state PC to a sulfoxide–PPh$_3$ adduct, thus accessing a ground-state Ir^{4+} complex (M$^+$/M, Scheme 1). This Ir^{4+} species (which is considerably more oxidizing than the corresponding *Ir^{3+} state) could afford the key phosphine radical cation **2** via phosphine oxidation (**1 → 2**), thus

enabling the earlier proposed radical chain reaction to proceed. Following sulfoxide attack (**2 → 4**) and β-scission (**4 → 6**), the resultant sulfide radical cation **6** could then undergo reduction in a number of ways: (1) reaction with PPh$_3$, thus regenerating phosphine radical cation **2** and propagating the radical chain (depicted in Scheme 3A); (2) reaction with the reduced sulfoxide–PPh$_3$ adduct; and (3) reaction with the excited-state PC to form the oxidizing ground-state Ir^{4+} complex, which would then go on to propagate initiation via phosphine oxidation (**1 → 2**) (2 and 3 are not depicted in Scheme 3A). We first sought to identify the formation of the proposed sulfoxide–PPh$_3$ adduct spectroscopically, but regrettably, no evidence for phosphine–sulfoxide interaction was evident using ^{1}H/^{31}P NMR or UV–vis spectroscopy (see the Supporting Information). Stern–Volmer quenching studies

Scheme 5. Biologically Active Sulfoxide Reduction[a,b]
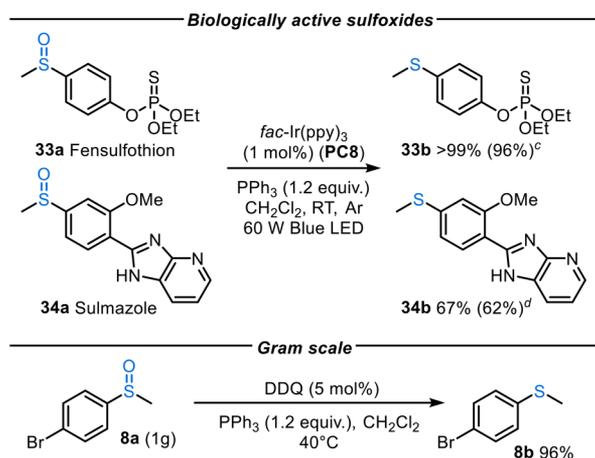
[a]Reaction conditions: sulfoxide (0.30 mmol), *fac*-Ir(ppy)$_3$ (1 mol %), PPh$_3$ (0.36 mmol) in CH$_2$Cl$_2$ (1.5 mL) at RT. [b]^{1}H NMR yields reported based on a trimethoxybenzene internal standard and isolated yields of products after column chromatography are shown in parentheses. [c]48 h reaction time. [d]24 h reaction time.

also revealed that a 1:1 mixture of PPh$_3$ and sulfoxide **8a** did not quench the emission of excited-state *fac*-Ir(ppy)$_3$ (**PC8**) even at concentrations far greater than that found in the reaction (Scheme 3B). We therefore turned to cyclic voltammetry to see if we could observe a reduction potential consistent with oxidative quenching of the excited state of **PC8**. More encouragingly, a unique reduction process was observed (with an onset potential of approximately −0.8 V vs Ag/AgCl) when both the sulfoxide and PPh$_3$ were present in solution, which was absent when either of these reagents was omitted (Scheme 3C). This electrochemical data certainly suggests that the redox chemistry of the sulfoxide and PPh$_3$ is affected by the presence/absence of the other. At present, these findings still leave some questions unanswered (most pertinently, what the structure of the hypothetical sulfoxide–PPh$_3$ adduct could be), but the synthetic and mechanistic results do support the notion that an alternative mechanism for deoxygenation operates when a PC with a sufficiently reductive potential is used.

Next, attention was turned to probing the synthetic utility of the deoxygenation. A preliminary substrate screen was conducted from which the relatively oxidizing photocatalyst **PC2** was identified as the most broadly effective PC (see the Supporting Information) and was taken into further substrate scoping studies (Scheme 4). Diaryl sulfoxides **9a**–**11a** were all well tolerated; notably, sulfoxide **11a**, incorporating an acid-sensitive Boc group, was converted into its sulfide **11b** in 99% yield. Various sulfoxides bearing a single functionalized aryl group also worked well, including halogenated systems (e.g., **8b** and **15b**). Sulfoxide **14a**, which contains an acid-labile silyl ether, was also an excellent substrate for this transformation, providing the corresponding sulfide **14b** in 90% yield.

Importantly, the freedom to vary the PC (and in particular, to vary its redox properties) allows deoxygenation to be performed on a wide range of substrates. For example, when using the most oxidizing photocatalyst Ir[(dF(CF$_3$)ppy)$_2$(d-(CF$_3$)bpy)]PF$_6$ (**PC1**), we were pleased to discover that sulfoxide **13a**, which contains an unprotected alcohol, afforded sulfide **13b** in 78% yield, which was a significant improvement upon the yield using **PC2**.[24] Sulfoxide **17a** also reacted poorly

with **PC2** under optimized conditions (34% conversion), with this attributed to competing oxidation of the benzothiazole moiety in this substrate. To address this, we tested the deoxygenation of sulfoxide **17a** using the less oxidizing *fac*-Ir(ppy)$_3$ photocatalyst **PC8**, and gratifyingly, the corresponding sulfide **17b** was isolated in near-quantitative yield, further demonstrating the value of having complementary synthetic protocols based on both oxidizing and reducing catalysts (see the Supporting Information for more comparisons between the reactivities of **PC2** and **PC8**).

Sulfoxide reduction was also performed on a wide range of dialkyl sulfoxides with varying alkyl chain lengths; all reactions progressed cleanly to furnish the desired linear (**18b**, **20b**, and **21b**) and cyclic (**19b**) sulfide products in excellent yields. Acetal protecting groups are also well tolerated by this procedure, with sulfide **24b** generated in 90% yield. Complete reduction of sulfoxide **25a** derived from *N*-Boc-protected methionine was also achieved, furnishing the corresponding sulfide **25b** in 99% isolated yield. A list of low-yielding or unreactive substrates is presented at the bottom of Scheme 4 (**26a**–**32a**). We believe that the low reactivities of these substrates can generally be attributed to poor solubility of the sulfoxide starting material in CH$_2$Cl$_2$ or low nucleophilicity of the sulfoxide/sulfone starting material. Interestingly, aryl carboxylic acid-containing sulfoxide **29a** undergoes deoxygenation when using **PC2** (38% yield), but incomplete conversion of the sulfoxide starting material is observed alongside the formation of a side product.[25] When performing the deoxygenation reaction using **PC8**, the corresponding sulfide is formed cleanly in 67% yield, with the remaining mass balance composed of unreacted sulfoxide. In all the above scoping studies, the only byproduct formed is triphenylphosphine oxide, and no discernible side products were isolated except where explicitly stated.

Finally, to further demonstrate the functional group tolerance and utility of the procedure, the deoxygenation of a sulfoxide-containing agrochemical (**33a**) and drug molecule (**34a**) was investigated (Scheme 5). In these examples, low to moderate yields of sulfide products were observed when using **PC2** under a range of conditions. However, upon switching to **PC8** (with a greater reduction potential), far superior reactivity was observed. Thus, agrochemical agent fensulfothion **33a**, which contains a phosphorothioate moiety, was cleanly reduced to its corresponding sulfide **33b** in 96% isolated yield. Furthermore, sulmazole **34a**, a cardiotonic drug containing an imidazopyridine ring, was converted into sulfide **34b** in 62% yield under the same conditions; this was a more challenging substrate due to its limited solubility in a range of solvents.

Scalability can be a concern in photoredox-catalyzed processes, with an increased photon flux needed for large-scale photochemical reactions. Advances in flow chemistry technology have come a long way in addressing this problem; however, larger-scale photochemical reactions are still typically less straightforward to achieve experimentally compared to the scale-up of thermal reactions.[26] To demonstrate that this phosphine radical cation strategy can easily be adopted by researchers who do not have access to the necessary equipment to perform photochemical flow reactions, deoxygenation of sulfoxide **8a** was performed on a 1 g scale, using DDQ as the radical chain initiator, affording sulfide **8b** in 96% yield, with the rest of the mass balance consisting of unreacted sulfoxide **8a**.

In conclusion, this study shows that phosphine radical cations can interact with sulfoxides via a polar/radical crossover mechanism. This novel reactivity could provide a basis for the development of new chemistry, exemplified here by our photocatalytic sulfoxide deoxygenation protocol. Using this mild, visible light-driven method, a wide array of functionalized sulfoxides can be reduced to the corresponding sulfides, including substrates containing acid-sensitive functional groups that are often incompatible with acidic conditions typically utilized in established methods for sulfoxide reduction. Complementary protocols based on a range of both oxidizing and reducing photocatalysts, which operate via different mechanistic pathways, further increase the range of substrates that can be accommodated.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.0c00690.

> Experimental procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(19) When sulfoxide **8a** was irradiated with a 3 W blue LED light using **PC2** with the conditions seen in Scheme 1, sulfide **8b** was formed in 65% yield based on a trimethoxybenzene internal standard.

(20) Examination of the reaction mixture for the conversion of **8a** into **8b** using **PC2** revealed that 1 mol % **PC2** remained, which was determined using ^1H NMR spectroscopy with a trimethoxybenzene internal standard. Furthermore, ^{19}F NMR spectroscopy revealed no new ^{19}F signals after the reaction, suggesting that the catalyst did not degrade or form aggregates during the course of the reaction (see the Supporting Information).

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